Columbia University
NOV
2
1905

Further Investigations in the Quinazoline Group.

DISSERTATION.

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF PURE SCIENCE OF COLUMBIA UNIVERSITY.

BY

HARVEY AMBROSE SEIL, B.A.

NEW YORK CITY.

1906.

3781
C72S

EASTON, PA.:
ESCHENBACH PRINTING COMPANY.

Further Investigations in the Quinazoline Group.

DISSERTATION.

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF PURE SCIENCE OF COLUMBIA UNIVERSITY.

BY

HARVEY AMBROSE SEIL, B.A.

NEW YORK CITY.

1906.

EASTON, PA.:
ESCHENBACH PRINTING COMPANY.

TABLE OF CONTENTS.

Acknowledgment 4
Historical Introduction..... 5
Methods of Preparation of Ketodihydroquinazolines 9
Properties of 4-Ketodihydroquinazolines..... 12
Introduction..... 13
Preparation of 6-Nitro-anthranilic Acid..... 17
Preparation of 4 Nitro-acetanthranilic Acid..... 17
Preparation of 6-Nitro-acetylanthranil..... 18
Preparation of 6-Nitro-propionyl-anthranilic Acid... 18
Preparation of 6-Nitro-propionyl-anthranil..... 18
Preparation of 4-Nitro-acetanthranil..... 19
Preparation of Acetanthranil. 19
Preparation of 3-Alkyl Quinazolines from the Anthranils..... 20
3-Alkyl 2-methyl-5-nitro-4-ketodihydroquinazolines..... 21
3-Alkyl 2-methyl 7-nitro-4-ketodihydroquinazolines..... 24
3-Alkyl-2-methyl-4-ketohydroquinazolines..... 25
Hydrazine on 6-Nitroacetanthranil..... 26
3-Amino-2-methyl-4-ketodihydroquinazoline 26
3-Amino-2-methyl-4-ketodihydroquinazoline Hydrochloride..... 26
3-Amino-2-methyl-4-ketodihydroquinazoline Chlorplatinate 27
3-Amino-4-ketodihydroquinazoline Diacetyl Derivative 27
3-Amino-4-ketodihydroquinazoline Brom Diacetyl Derivative..... 27
3-Amino-4-ketodihydroquinazoline Phenylhydrazone..... 27
3-Amino-4-ketodihydroquinazoline Uramino Derivative..... 28
Reactions of the Aminoquinazoline..... 29
Diquinazolyl..... 31
Oxygen Ethers..... 31
Summary..... 33
Bibliography..... 35
Biographical.. 37

ACKNOWLEDGMENT.

This work was undertaken at the suggestion of Professor Marston T. Bogert and carried out under his direction.

I take this opportunity to gratefully acknowledge my indebtedness to him for his valuable assistance and advice throughout the work and to express my thanks for his encouragement given to the research, his interest in its progress and for other valuable assistance rendered. H. A. S.

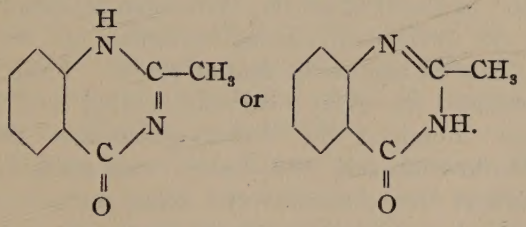
ORGANIC CHEMICAL LABORATORY
HAVEMEYER HALL, COLUMBIA UNIVERSITY,
May, 1906.

HISTORICAL INTRODUCTION.

In 1878 Griess[1] obtained 2 cyan. 4-ketodihydroquinazoline by passing cyanogen gas into a saturated water solution of anthranilic acid. In 1885 the same author[2] made a more complete investigation of this reaction and prepared a series of derivatives by changes in the cyan. residue. In the same year Weddige[3] showed that fusion of acyl ortho-amino-benzamid yielded alkyl 4-ketodihydroquinazoline. Two years later he[4] showed that ketoquinazolines could be obtained from acyl ortho-amino-benzamid 1, by fusion; 2, by treatment with dilute caustic potash; 3, by long boiling with water. He also showed that the ethyl ester of acyl ortho-amino-benzoic acid, when heated in a bomb with aqueous ammonia, yielded a quinazoline and that with alcoholic ammonia no condensation took place.

Weddige obtained the alkyl 4-ketodihydroquinazoline by treating one molecule of the 2-methyl-4-oxy-quinazoline in alcoholic solution with one molecule of potassium hydroxide and one of methyl iodide by boiling under a reflux condenser for two hours on the water-bath.

Two structures were possible for the product from the (*o*)-acetamine benzamid.



(1) (2)

which might react its enolic form.

Weddige proved (2) to be the correct structure by comparison of the two dimethyl derivatives possible. He showed that the dimethyl derivative obtained by the fusion of ortho-amino-benzmethyl-amid corresponded exactly with the dimethyl quinazoline obtained before, while the dimethyl quinazoline made by

fusing (*o*)-methylamino-benzamid gave a melting-point 90° higher. From the synthesis of 2.3-dimethyl quinazoline from the ortho-amino-benzmethylamid and from the potassium salt of the (2) methyl-4-oxy-quinazoline, he concluded formula (2) to be the correct one.

In 1889 Nimentowski[5] prepared tolyl quinazolines by treating homoanthranilic amid with acids or acid anhydrides.

Paal and Busch[6] in 1889 prepared 4-ketodihydroquinazoline by the oxidation of the corresponding dihydroquinazoline with potassium permanganate. In the following year Dehoff[7] succeeded in nitrating the (2) methyl- (3) hydrogen- (4) keto-dihydroquinazoline first made by Weddige, as well as the 2-3-dimethyl quinazoline. The latter he also prepared by the etherification of his first product with alcoholic caustic potash and methyl iodide. He could not, however, determine the position of the nitro group. With phosphorus pentachloride he obtained a tetrachlor derivative, which on treatment with alcoholic caustic potash reverted to the trichlor 2-methyl-4-oxy-dihydroquinazoline. The tetrachlor derivative on treatment with primary amines yielded the corresponding monamino compounds.

In 1891 Knape,[8] by heating the methyl hydrogen quinazoline with methyl iodide in a bomb tube, obtained the iodide of the methyl ammonium base which, on treatment with damp silver oxide, yielded the hydroxy ammonium compound. He also obtained the ortho-oxalyl-amino-benzamid by the action of methyl oxalate on anthranilic acid at 170° C. From this derivative he obtained the 4-oxy-2-carbonic methyl ester quinazoline.

Zacharias[9] obtained the 8-nitro-quinazoline from the 3-nitro-acetanthranilic acid ethyl ester with alcoholic ammonia. This compound formed no salts with acids, ammonia or platinum tetrachloride but formed a definite potassium and silver salt. He also prepared the dimethyl and the corresponding phenyl derivatives. He succeeded in reducing the nitro group by two methods: (1) by tin or stannous chloride and hydrochloric acid; (2) by ammonium sulphide.

In the same year Thieme[10] carried out the reactions of primary amines on the ethyl ester of the 5-nitro-acetanthranilic

acid, obtaining the same derivatives which Dehoff[7] had prepared, fixing the nitro group in the six-position.

Paal and Krecke,[11] by oxidation of the 2-methyl-3-phenyl-dihydroquinazoline in alkaline potassium permanganate, prepared the 2-carboxyl-3-phenyl-quinazolon, which readily lost carbon dioxide, passing to the 3-phenyl-quinazolon.

In 1893 Bischler and Burkart[12] obtained 4-ketoquinazolines by heating the ammonium salt of the acyl-(*o*)-amino-anthranilic acid. The yields were small. The derivatives checked in properties and melting-points with those prepared by Weddige.[4]

Niementowski[13] in 1895 discovered that when anthranilic acid was heated with aliphatic acid amides oxy-quinazolines were produced. He found the reaction most efficient with formamid, the efficiency of the reaction decreasing with the increase in molecular weight of the acid amid used. With benzamide or other aromatic amides no quinazolines were obtained.

Bischler and Lang[14] prepared a series of ketoquinazolines by oxidation of the 2-akyl quinazoline, dissolved in glacial acetic acid, with two moles of chromic acid.

In the year 1897 McCoy[15] converted the mono-thio-phenyl benzoylene urea into the corresponding chlor derivative by the action of dry chlorine in the presence of chloroform. On condensing this product with anilin he obtained the corresponding 2-anilino derivative. From the same thio-quinazoline by etherification with caustic alcoholic alkali and ethyl iodide he prepared the 2-mercapto-3-phenyl-quinazolon, which, on boiling with hydrochloric acid, split off ethyl mercaptan.

In 1900 Bogert and Gotthelf,[16] by the action of nitriles on anthranilic acid in a bomb, found a convenient method for the preparation of the 2-alkyl-4-oxy-quinazolines. The products obtained agreed in their properties with those prepared by Weddige,[4] Bischler and Lang[14] and Niementowski.[13]

In 1902 Bogert and Hand[18] showed that quinazolines are readily prepared by warming acylanthranilic nitriles with alkaline hydrogen dioxide solution. This method gives the quinazoline directly without isolating the intermediate amid.

Anschutz Schmidt and Greiffenberg[17] first studied the action of primary amines on anthranils. With aliphatic amines the condensation stopped at the amide state which was converted to the closed ring by boiling with caustic potash. With aromatic amines, however, the quinazoline was obtained directly. This was by far the most convenient way of obtaining 4-ketoquinazolines, in good yield and in almost pure condition.

In 1903 Pawliewski[19] modified Niementowski's[13] method for preparing quinazolines with acid amides. He succeeded in preparing 2-phenyl-4-oxy-quinazoline by heating anthranilic acid with thio-benzamide. Niementowski could get no reaction with aromatic acid amides.

In 1904 Thode[20] prepared 3-amino-quinazolons by boiling (*o*)-amino-benzhydrazid with the calculated quantity of formic acid. From this amino derivative he prepared the benzaldehyde and salicyl aldehyde substitution products.

In the same year Gartner[22] obtained the 2-alkyl-quinazolon by the action of ammonia on 2-dichlor-methyl-4-keto-benzmetoxazoline. On condensing this derivative with phenylhydrazine he obtained both a substitution of the chlorine by the phenhydrazino radical and the replacement of the (3) hydrogen by the anilino.

In 1904 König[21] duplicated the work of Bogert and Gotthelf on the action of nitriles on anthranilic acid. He carried out reactions with α-toluic nitrile and also with succinic nitrile. From the latter he obtained a diquinazolon ethane by condensing it with two molecules of anthranilic acid. He showed also that the imid hydrogen in position (3) could be replaced by the benzoyl residue by reaction in pyridin solution of one molecule of 2-alkyl-4-quinazolon with one of benzoyl chloride.

In 1905 Bogert and Chambers[23] prepared 6-nitro-acetanthranil directly from the 6-nitro-anthranilic acid by condensation with acetic anhydride. This was found to be more reactive than the acetanthranil of Anschutz Schmidt and Greiffenberg. The action of ammonia and anilin on the anthranil was studied and the corresponding quinazolines obtained.

In a second paper[27] the authors reduced the nitro-quinazo-

line to the amino and studied its properties, preparing a series of characteristic derivatives.

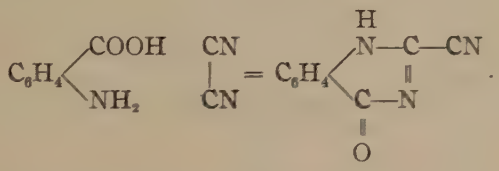
Bogert and Steiner[24] carried out reactions corresponding to the above by condensing 4-nitro-acetanthranil with primary amines and obtaining 7-nitro-quinazolines.

Bogert and Hand,[25] working with 5-brom-acetanthranil by condensations with primary amines, prepared a series of 6-brom-quinazolines.

Bogert and Hoffman obtained 7-methyl quinazolines by heating the acyl-homoanthranilic nitrile with alkaline hydrogen peroxide solution, a reaction which had previously been devised by Bogert and Hand.

Methods of Preparation of Ketodihydroquinazolines.

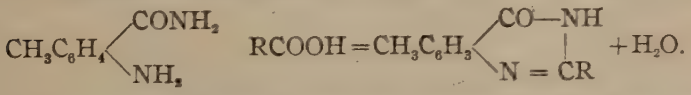
(1) Passing cyanogen gas into a saturated water solution of anthranilic acid (1).



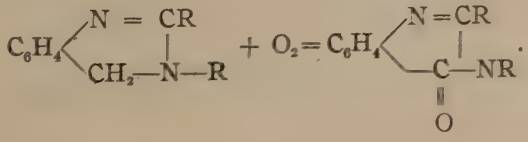
(2) By fusion of acyl (*o*)-amido-benzamid (3).

(3) By long boiling or treatment with dilute alkali of acyl-(*o*)-amido-benzamid (4).

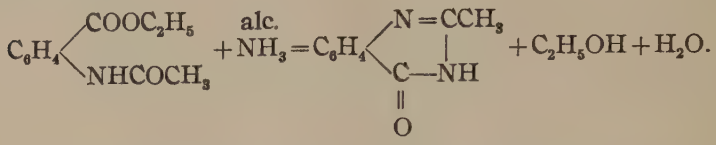
(4) Boiling anthranil-amide with acids or acid anhydrides (5).



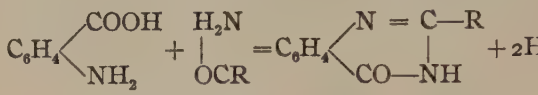
(5) Oxidation of the dihydroquinazoline to the ketohydro-quinazoline (6).



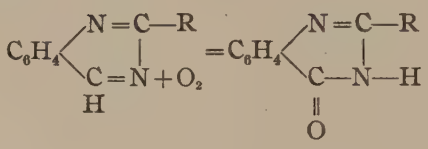
(6) Action of primary amines on the ethyl ester of acetanthranilic acid (9) (10).



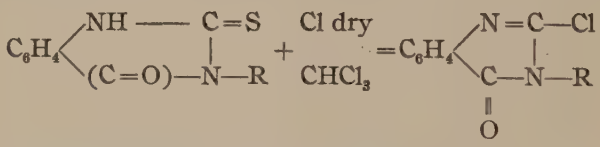
(7) Action of aliphatic acid amides on anthranilic acid (13).



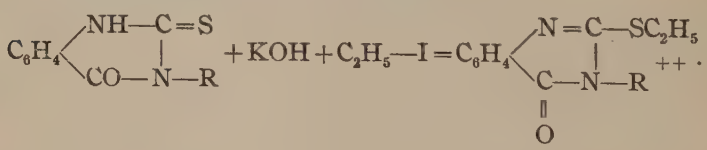
(8) Oxidation of 2-alkyl quinazolines to 2-alkyl ketodihydroquinazolines (14).



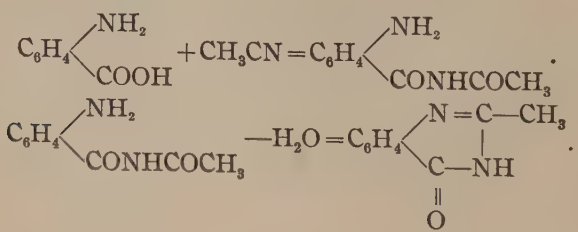
(9) Conversion of thio-benzoylene urea to ketodihydroquinazoline (15).



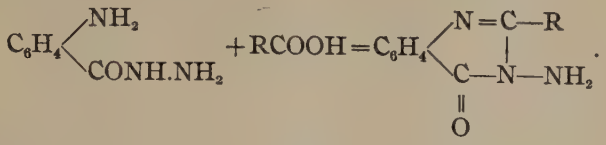
(10) Esterification of thio-benzoylene urea (15).



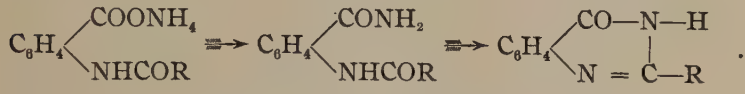
(11) Action of nitriles on anthranilic acid (16).



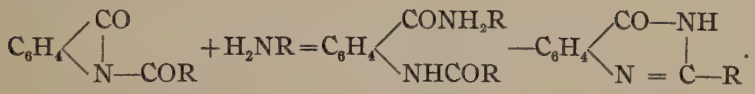
(12) Boiling orthoamino-benzhydrazid with acids (20).



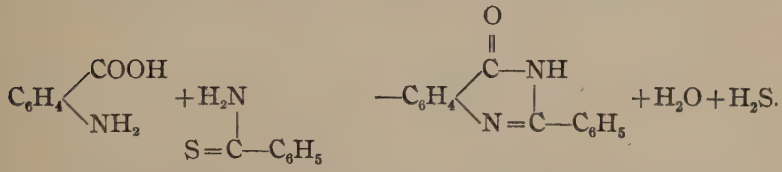
(13) By fusion of the ammonium salt of acyl-*o*-amino-benzoic acid (12).



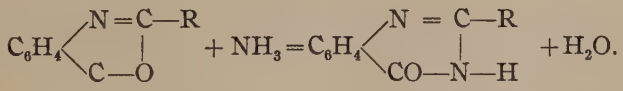
(14) By the action of primary amines on acyl-anthranil (17) (23) (24).



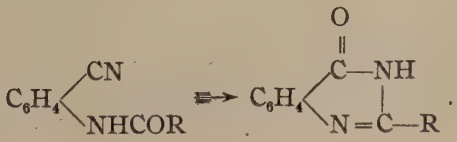
(15) By heating anthranilic acid with thio-benzamid (19).



(16) By condensation of keto-benzometoxazoline with ammonia (22).



(17) By warming acyl-anthranilic nitriles with alkaline hydrogen peroxide solution (18).



Properties of 4-ketodihydroquinazolines.

The 4-ketodihydroquinazolines are white crystalline solids generally insoluble in water and soluble in alcohol and ether. Two classifications can be made. The 2-3-dialkyl and the 2-alkyl-3-hydrogen quinazolines. The former are insoluble in acids and alkalies while the latter, due to the presence of the imino group, are soluble in acids and form salts with the strong acids, *viz.*, hydrochlorides, nitrates, sulphates, chromates, picrates, etc. These are easily hydrolyzed and readily revert to the quinazoline base. They form also alkaline salts in which case the quinazoline probably reacts in its enolic form. The alkaline salts (4) when treated with methyl iodide in alcoholic solution yield the 3-alkyl nitrogen ethers. With the heavier metallic salts, the hydrogen quinazolines yield voluminous precipitates containing both heavy metal and quinazoline.

With platinic chloride, well-defined, yellow crystals of the chlorplatinate are formed analogous to ammonium chlorplatinate.

When treated in pyridin solution with benzoyl chloride in molecular proportions the benzoyl group substitutes the imid hydrogen.

When treated with nitric acid, nitration takes place (7). Both the dialkyl and alkyl hydrogen quinazolines can be nitrated. With phosphorus pentachloride under pressure, chlorination takes place, three chlorines substituting on the benzene nucleus, and one on the pyrimidine ring replacing the enolic hydroxyl. This latter chlorine atom has the nature of an acid chloride and is therefore readily hydrolyzed by alkali, while the chlorine atoms on the benzene ring retain their usual stability toward reagents.

When oxy-quinazolines are treated with phospho·us oxychloride under ordinary pressure, but one chlorine atom substitutes and the chloride is obtained. This is readily hydrolyzed and the quinazoline regenerated. With sodium alcoholate the alkoxy-quinazolines are formed. The 4-chlor-quinazoline obtained by treating the 4-ketodihydroquinazoline with phosphorus oxychloride is reduced by red phosphorus and hydriodic acid to the quinazoline base.[28] Quinazoline thus

obtained, when subjected to vigorous oxidation, passes first to the ketodihydroquinazoline and then by the oxidation of the benzene ring, analogous to the case of naphthalene, pyrimidine dicarbonic acid is formed.

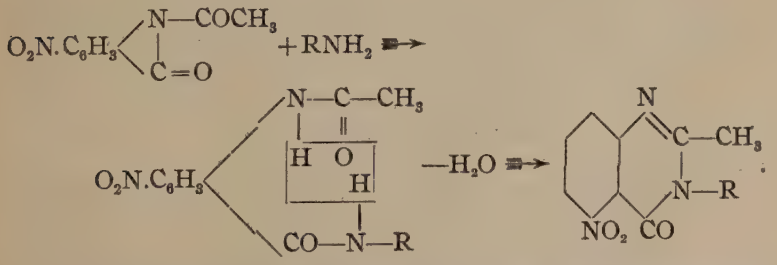
With methyl iodide the 2-alkyl-3-hydrogen-4-ketodihydroquinazoline forms an addition product, forming an iodide of the ammonium base (8). When treated with damp silver oxide the hydroxy ammonium base is formed.

The dialkyl ketoquinazolines, in which one alkyl group is aliphatic, on oxidation in glacial acetic acid with chromic acid, yield first the carbonic acid which readily loses carbon dioxide and reverts to the hydrogen quinazoline (11).

INTRODUCTION.

All four of the Bz-nitro-2-alkyl-4-ketodihydroquinazolines have already been prepared; the 5-nitro compounds by Bogert and Chambers;[23] the 6-nitro by Dehoff[7] and Thieme;[10] the 7-nitro by Bogert and Steiner;[24] and the 8-nitro by Zacharias.[9] But three of the (5)-nitro derivatives have been prepared. The work herein undertaken deals mainly with the completion of this series as well as some additions to the 7-nitro and unsubstituted quinazoline series.

Bogert and Chambers[23] have shown that quinazolines can be readily obtained from 6-nitro-acetanthranil and primary amines, the reactions involved being as follows:



They carried out this synthesis only with ammonia and with anilin. This article records similar syntheses with the following

primary amines: methyl, ethyl, normal and isopropyl, iso and secondary butyl, isoamyl and allyl on the 6-nitro-acetanthranil; ammonia, methyl and ethyl amine on 6-nitro-propionylanthranil; ethyl and isoamyl on the 4-nitro-acetanthranil and ammonia and methyl amine on the unsubstituted acetanthranil—thus demonstrating the general applicability of the reaction to primary aliphatic amines.

It will be seen from the above exhibition of the reaction how a primary amine condenses with the nitro-acetanthranil to form a quinazoline of the character of the "R." As a further corroboration of this fact the nitro-anthranil was condensed with hydrazine or diamine. Two possibilities are apparent: condensation with one amino group or with both amino groups. This was found to be the case. The 5-nitro-2-akyl-3-amino-4-ketodihydroquinazoline was formed by the reaction of one molecule of 6-nitro-acetanthranil with one of hydrazine and the 2,2′-dimethyl-5,5′-dinitro-4,4′-diketotetrahydrodiquinazolyl was obtained similarly by the condensation of two molecules of 6-nitro-acetanthranil with one of hydrazine.

The amino-quinazoline was separated from the diquinazolyl by its solubility in water and alcohol, in which the diquinazolyl is practically insoluble. Its hydrochloride, chlorplatinate, diacetyl, bromdiacetyl, phenylhydrazone and uramino derivatives were studied as well as its reactions with nitrous acid, potassium hydroxide and benzaldehyde.

The diquinazolyl was found to be rather inactive on account of its great insolubility. The only satisfactory solvent for crystallization is a mixture of equal parts of alcohol and acetone. When crystallized from acetic anhydride the elements of acetic anhydride add on. This is in accordance with the work of Heller.[29] It is unaffected by potassium hydroxide and forms no salts with acids and no substitution products with bromine.

The etherification reaction, first carried out by Weddige in which he obtained the 3-methyl quinazoline by treating the 2-methyl-4-ketodihydroquinazoline with alcoholic potassium hydroxide and methyl iodide was also investigated. Since the alkaline salt of the quinazoline must be in the enolic form, on

treatment with methyl iodide the corresponding alkyloxy-quinazoline should be obtained. Weddige showed that under these conditions with methyl iodide the 3-methyl quinazoline was always obtained, but the action of other alkyl iodides was not investigated.

In the present work the methoxy derivative was not obtained but the ethoxy derivatives of both the 5- and 7-nitro-quinazolines as well as the isoamyl oxygen ether of the 7-nitro was obtained. They were prepared as follows: The 2-methyl-4-ketodihydroquinazoline was dissolved in alcohol, the requisite amount of metallic sodium was added and after the reaction was over the theoretical amount of alkyl iodide was added.

First.—The mixture in a small flask was heated under a reflux condenser. The time required for complete reaction varied. The progress of the reaction could be ascertained, however, by testing the alcoholic mother-liquor with litmus paper to neutral reaction.

Second.—The mixture was placed in a bomb and heated from three to five hours at 150°. In no case could a pure methoxy derivative be obtained. But ethoxy derivatives of both the 5- and 7-nitro-quinazolines were obtained by both methods. The isoamyl ether of the 7-nitro was also obtained by both methods. The ethers are white crystalline solids of lower melting-point than the corresponding nitro in ether isomers. The crystalline forms resemble those of their isomers except that of the isoamyl ether which crystallizes in flat plates while the isomeric quinazoline crystallizes in long needles. The isoamyl ether on treatment with hydrochloric acid decomposed into the methyl hydrogen quinazoline while the nitrogen isomeric quinazolines form salts with hydrochloric and other strong acids.

Experimental.

6-nitroanthranilic acid-3-nitro-(*o*)-phthalic acid was prepared by the direct nitration of phthalic anhydride.[30] If the initial reaction becomes too violent the phthalic anhydride may be entirely destroyed. The yield of the pure 3-nitrophthalic acid is about one-third that of the anhydride originally taken. More may be recovered from the mother-liquors, but this is generally

contaminated by the 4-nitro isomer. A better plan is to take the mixture of the 3- and 4-nitrophthalic acids, crystallize it once from water, to free it from free sulphuric and nitric acids, dissolve in methyl alcohol and then pass in dry hydrochloric acid gas. The 4-nitro acid forms a neutral dimethyl ester while the 3-nitro acid forms an acid methyl ester which can be separated by its solubility in alkaline carbonate solution.

The 3-nitro-(*o*)-phthalic is next converted into the 3-nitrophthalimide by the following methods:

(1) The action of ammonia gas on the fused anhydride.[31]

(2) Heating the acid ammonium salt.[23]

(3) Heating the neutral ammonium salt.

(4) Adding an excess of ammonia to the acid methyl ester, evaporating to dryness and fusing the residue.

The first of these meth ds proved to be the least satisfactory, both as to yield and quality of product. The others all gave good yields and good products. The advantage of the third and fourth methods is that an excess of ammonia can be used and the preparation of a pure acid ammonium salt thus obviated. As the (3)-nitrophthalic acid is frequently separated from the 4-nitro acid by conversion into the acid methyl ester the application of the fourth method is evident.

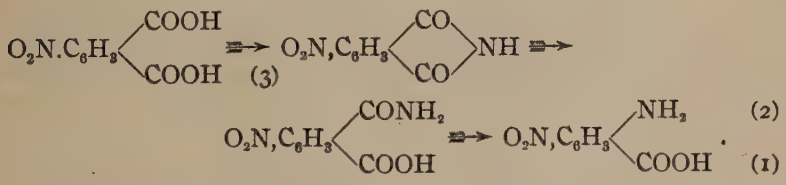
The third and fourth methods are carried out in much the same way. The acid or acid ester is treated with an excess of ammonia and evaporated to dryness at 110°. The temperature is then raised to 170–180° until no more ammonia is evolved and then to 210° until fusion occurs. When the fused mass has ceased to effervesce the temperature is raised for a few minutes to 216° and the melt is then allowed to cool. The crude imide from the acid methyl ester forms large yellow lustrous needles, melting sharply at 216° and is practically pure. That from the neutral ammonium salt melts at 210–216° and is easily purified by crystallization from alcohol and acetone. At times a product was obtained melting between 186–190° whose melting-point could not be raised by recrystallization. It resembled the imide in its physical appearance, being yellow in color and crystallizing in slender needles. Its constitution was not determined.

The imide is converted into the amic acid by caustic potash

by Kahn's method.[31] The imide and the requisite amount of standard alkali are stirred by a turbine for two to three hours. The solution of the potassium salt of the amic acid thus obtained is well cooled and the calculated quantity of hydrochloric acid added slowly. If the amic acid does not separate in five minutes after the hydrochloric acid has been added a handful of salt thrown in materially assists in the separation. The yield is from 78 to 80 per cent. of the weight of imide used.

By means of the Hoffman reaction using caustic potash and bromine on the amic acid, the 6-nitro-anthranilic acid is obtained.[31] The ice-cold solution of bromine in caustic potash is added to the cold solution of the amic acid dissolved in the alkali with constant shaking. The cold solution of a light yellow color is then placed on the boiling water-bath and heated as rapidly as possible. The close of the reaction is marked by the development of a deep red color and takes from twenty-five to thirty-five minutes. The solution is then placed into an ice-bath and when cold carefully acidified with the calculated quantity of hydrochloric acid. The amino acid separates in yellow glistening crystals. If the boiling has taken place too slowly or has been prolonged after the change to the red color, the acid may separate in the granular condition, but as a rule no crystals are obtained and a semi-solid mass results. The yield is good, 80–85 per cent. of the weight of the amic acid taken.

The preparation of the 6-nitro-2-amino-benzoic acid takes place according to the following scheme:

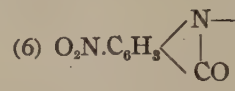


(4)-Nitro-acetanthranilic acid[24] (*o*)-toluidine was nitrated in the presence of a large excess of concentrated sulphuric acid by the method of Nölting and Collin. The crude dry 4-nitro-2-toluidine is then boiled a few minutes with acetic anhydride and allowed to cool somewhat and then poured into alcohol. Crystal-

lization takes place in a short time and yields comparatively pure nitro-acettoluide. This product is oxidized by potassium permanganate in the presence of magnesium sulphate to insure a neutral solution. On acidification of the alkaline salt an 80 per cent. yield of the practically pure acid is obtained.

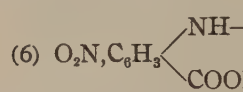
PREPARATION OF ANTHRANILS.

6-*Nitro-acetylanthranil,*



—This had already been prepared by Bogert and Chambers.[23] 6-Nitro-acetanthranilic acid is dissolved in acetic anhydride and boiled a few minutes. On cooling, almost pure white crystals of the anthranil separate. The properties coincide with those found by Bogert and Chambers.

6-*Nitro-propionyl-anthranilic acid,*



—This is prepared by dissolving 6-nitro-anthranilic acid in freshly distilled propionic anhydride and boiling a few minutes. On cooling, white crystals are obtained which contain a mixture of the 6-nitro-propionyl-anthranil and 6-nitro-propionyl-anthranilic acid. On crystallization from ethyl acetate, beautiful hard compact crystals of the acid are obtained, melting-point 218 (corr.).

The properties of this acid follow those of the 6-nitro-2-acetamino-benzoic acid of Bogert and Chambers.[23] It is easily soluble in hot alcohol or ethyl acetate, sparingly soluble in warm chloroform, carbon tetrachloride or benzene and insoluble in ether.

Calculated for $C_{10}H_{10}O_5N_2$: N, 11.76. Found: N, 11.85.

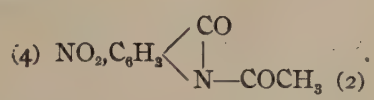
6-*Nitro-propionyl-anthranil,*

—On attempting to prepare this compound in the same way as the 6-nitro-acetylanthranil by dissolving the 6-nitro-anthranilic

acid in propionic anhydride, no pure product could be isolated, a mixture of anthranil and 6-nitro-propionyl-anthranilic acid resulting. On crystallization from ethyl acetate the pure propionyl anthranilic acid results. On boiling this with acetic anhydride and freezing in an ice-bath a mixture as above is always obtained. If, however, an excess of anhydride is used, and then the excess evaporated, whereby the acetic acid formed by the reaction is removed, the anthranil crystallizes out. The essential condition is to remove almost all of the acetic anhydride solvent and then cool quickly. The anthranil crystallizes in almost white compact crystals which melt at 90°. It resembles the 6-nitro-acetylanthranil in its properties and is more readily hydrolyzed.

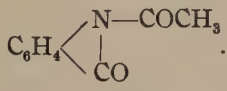
Calculated for $C_{10}H_8O_4N_2$: N, 12.72. Found: N, 12.21, 12.37.

4-Nitro-acetanthranil,



—This had previously been prepared by Bogert and Steiner.[24] The method of procedure is the same as with the 6-nitro-acetanthranil. The 4-nitro-acetanthranilic acid is boiled with a slight excess of acetic anhydride and allowed to crystallize. Generally, the anthranil is obtained in small yellow crystals but when absolutely pure almost colorless crystals are obtained, melting-point 131–138 (corr.).

Acetanthranil,



—Anschütz Schmidt and Greiffenberg[17] were the first to prepare this compound. It s readily obtained by boiling anthranilic acid with acetic anhydride and allowing to cool when well-defined crystals of the acetanthranil form. A strong odor of acetamide is noticeable during the reaction. The properties of the acetanthranil coincide with those found by Anschütz Schmidt and Greiffenberg.

PREPARATION OF 3-ALKYL QUINAZOLINES FROM THE ANTHRANILS.

The general method of procedure is as follows: Five grams of the anthranil are placed in a flask with a slight excess of an aqueous (1:3) solution of the primary amine. Considerable heat is evolved (the reaction with the pure amine is generally too violent), and the solution becomes colored. This color varies from a yellow with methyl amine to a red with isoamyl amine. When the first reaction is over, the flask is heated two or three minutes on the steam-bath, and then allowed to cool. Most of the quinazoline separates as a precipitate in the flask, contaminated with some of the intermediate amide. The mixture is made silghtly acid with acetic acid and filtered. The precipitate of quinazoline is freed from amide by washing it with cold dilute caustic potash and the alkaline washings are added to the mother-liquor. The combined mother-liquor and alkaline washings should be slightly alkaline (too strong alkali gives a red color). By boiling this alkaline solution all amide is changed to quinazoline and precipitated at once. This precipitate is combined with the first crop of quinazoline and the two purified together by crystallization from alcohol.

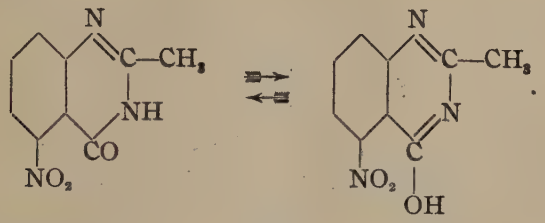
The following method of converting the amide into quinazoline was also tried: after the completion of the reaction between the anthranil and the amine the mixture is evaporated to dryness at 100°. The temperature is then raised to 150° and kept there till the cessation of all effervescence (about four hours) when it is allowed to cool. A brown cake results from which the pure quinazoline is obtained only after frequent crystallizations from alcohol in the presence of bone-black. The yield is very poor.

Weddige[4] has shown that acylanthranil amides pass into quinazolines on boiling with water or with alkalies or when fused.

The 3-alkyl quinazolines are all white crystalline solids, the majority having high melting-points. The allyl derivative is dimorphous. All except the quinazolines obtained by ammonia carry hydrocarbon radicals in positions 2 and 3 and are therefore insoluble in alkalies. In general, they are insoluble or difficultly soluble in water, carbon tetrachloride, carbon disulphide, petroleum ether, cold benzene or cold ether; moderately soluble in the

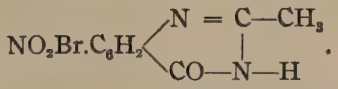
two latter solvents at the boiling-point, or in cold methyl, ethyl or isoamyl alcohols or in cold acetone; easily soluble in the four latter solvents at the boiling-point and in chloroform or ethyl acetate Beautiful crystals of the quinazoline may be obtained by dissolving the quinazoline in a slight excess of boiling strong alcohol, adding water carefully to the hot solution until it begins to cloud and then allowing the solution to cool.

2-Methyl-5-nitro-4-ketodihydroquinazoline (*2-methyl-5-nitro-4-oxyquinazoline*),



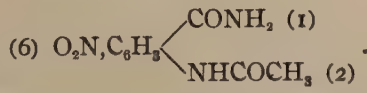
—This was prepared from 6-nitro-acetanthranil and ammonia as already described by Bogert and Chambers.[23] As it contains a replaceable (enolic) hydrogen, it dissolves freely in alkalies. It is also moderately soluble in water. In these respects it differs from the dialkyl-quinazolines which follow:

Brom-2-methyl-5-nitro-4-ketodihydroquinazoline,



—This is made by dissolving the methyl hydrogen quinazoline in acetic anhydride and adding an excess of bromine in the same solvent. On warming a few minutes a white precipitate of the brom derivative is formed. This is filtered and recrystallized from alcohol. Small, hard compact crystals are obtained which darken at 240 and do not melt at 340°. Nitrogen found, 14.68. Calculated for $C_6H_6N_3Br$, 14.78.

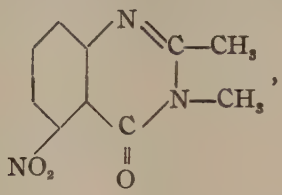
6-Nitro-acetanthranil amide,



—This is the intermediate product in the above condensation

and was isolated in one of the experiments. It is a white crystalline substance melting at 218–219° (corr.) and dissolves in dilute alkalies. On heating its alkaline solution, it is changed to the quinazoline which remains in solution as the alkaline salt and can be precipitated by passing in carbon dioxide.

2 3-*Di-methyl-5-nitro-4-ketodihydroquinazoline*,

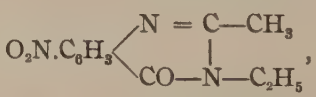


from 6-nitro-acetanthranil and methyl amine, melts at 203° (corr.).

Calculated for $C_{10}H_9O_3N_3$: C, 54.79; H, 4.11; N, 19.17. Found: C, 54.43, 54.51; H, 4.08, 4.16; N, 19.24, 19.31.

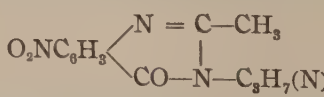
Hydrochloride: On dissolving the dimethyl quinazoline in an excess of alcohol and adding one-third the volume of concentrated hydrochloric acid, crystals of the hydrochloride are deposited. These are small and granular in distinction to the long needles of the quinazoline. It is hydrolyzed by boiling water, melting-point 250° C. (uncorr.).

2-Methyl-3-ethyl-5-nitro-4-ketodihydroquinazoline,



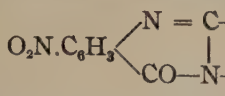
from 6-nitro-acetanthranil and ethylamine melts at 208° (corr.). Calculated for $C_{11}H_{11}O_3N_3$: N, 18.00. Found: N, 17.87.

2-Methyl-3-n-propyl-5-nitro-4-ketodihydroquinazoline,



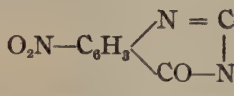
from 6-nitro-acetanthranil and normal propylamine, melts at 204–205° corr.). Nitrogen found, 16.93. Calculated for $C_{12}H_{13}O_3N_3$, 17.00.

2-Methyl-3-(i)-propyl-5-nitro-4-ketodihydroquinazoline,



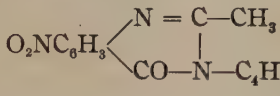
from 6-nitro-acetanthranil and isopropyl amine, melts at 219–220° (corr.). Nitrogen found, 16.88. Calculated for $C_{12}H_{13}O_3N_3$, 17.00.

2-Methyl-3-(i)-butyl-5-nitro-4-ketodihydroquinazoline,



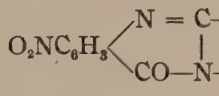
from 6-nitro-acetanthranil and isobutyl amine, melts at 202–203° (corr.). Nitrogen found, 16.08. Calculated for $C_{13}H_{15}O_3N_3$, 16.09.

2-Methyl-3-secondary butyl-5-nitro-4-ketodihydroquinazoline,



from 6-nitroacetanthranil and secondary butylamine, melts at 209–210° (corr.). Nitrogen found, 15.84. Calculated for $C_{13}H_{15}O_3N_3$, 16.09.

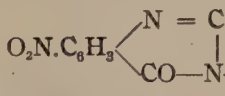
2-Methyl-3-(i)-amyl-5-nitro-4-ketodihydroquinazoline,



from 6-nitro-acetanthranil and isoamyl amine, melts at 213–214° (corr.).

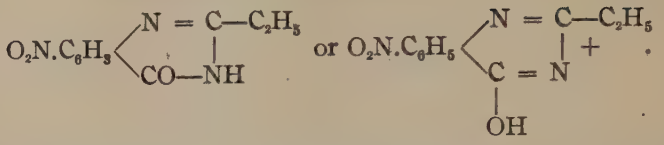
Found: C, 60.82, 60.74; H, 6.12, 6.41; N, 15.17, 15.35. Calculated for $C_{14}H_{17}O_3N_3$: C, 61.09; H, 6.18; N, 15.27.

2-Methyl-3-allyl-5-nitro-4-ketodihydroquinazoline,



from 6-nitro-acetanthranil and allyl amine, melts at 160–161° (corr.). It is dimorphous, crystallizing in rhombic plates or long needles. Nitrogen found, 16.95. Calculated for $C_{12}H_{11}O_3N_3$, 17 14.

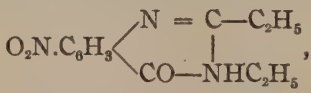
2-Ethyl-5-nitro-4-ketodihydroquinazoline.



—From 6-nitro-propionyl-anthranil and ammonia: Since it contains an enolic hydrogen, it dissolves in al alies and is reprecipitated by carbon dioxide. It is less soluble in water than the 2-methyl-4-ketodihydroquinazoline.

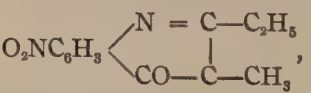
The best solvent is water and alcohol. Its melting-point is 240° (corr.). Nitrogen found, 19.31. Calculated for $C_{10}H_9O_3N_3$, 19.17.

2,3-Diethyl-5-nitro-4-ketodihydroquinazoline,



from 6-nitro-propionyl-anthranil and ethylamine, melts at 181° (corr.). Found: C, 57.97; H, 5.01; N, 17.19. Calculated for $C_{12}H_{13}O_3N_3$: C, 58.29; H, 4.85; N, 17.00.

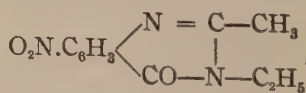
2-Ethyl-3-methyl-5-nitro-4-ketodihydroquinazoline,



from 6-nitro-propionyl-anthranil and methyl amine, melts at 197–198° (corr.). Nitrogen found, 18.09. Calculated for $C_{11}H_{11}O_3N_3$, 18.00.

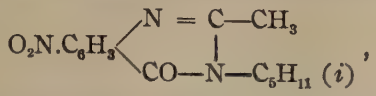
7-NITRO-QUINAZOLINES.

2-Methyl-3-ethyl-7-nitro-4-ketodihydroquinazoline,



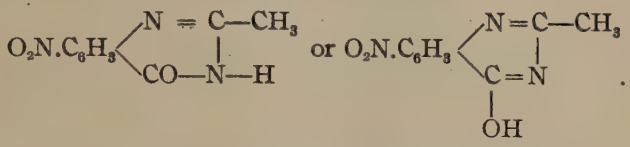
from 4-nitro-acetanthranil with ethyl amine, melts 175° (corr.). Nitrogen found, 17.85. Calculated for $C_{11}H_{11}O_3N_3$, 18.00.

2-Methyl-3-isoamyl-7-nitro-4-ketodihydroquinazoline,



from 4-nitro-acetanthranil and isoamyl amine (melts at 117–118°) at first forms a light yellow oil, which, on bone-blacking in alcohol solution, forms slender crystals. Nitrogen found, 15.09. Calculated for $C_{14}H_{17}O_3N_3$, 15.27.

2-Methyl-7-nitro-4-ketodihydroquinazoline,

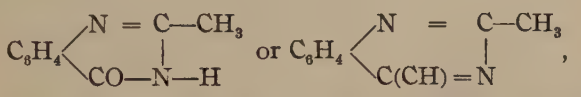


—This was prepared from 4-nitro-acetanthranil and ammonia as already described by Bogert and Steiner.[24]

It resembles the 2-methyl-5-nitro-4-ketodihydroquinazoline in its properties. It melts at 275–277° (corr.).

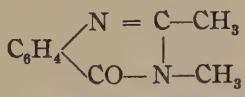
UNSUBSTITUTED QUINAZOLINES.

2-Methyl-4-ketodihydroquinazoline,



from acetanthranil with ammonia. This had already been prepared by Weddige[4] by fusion of the ortho-acet-amido-benzamid. The product obtained from the anthranil is identical with that obtained by the fusion of the amide.

2,3-Dimethyl-4-ketodihydroquinazoline,



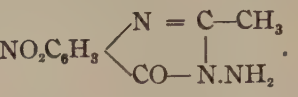
from acetanthranil and methyl amine, melts first at 72° then at 108–109° (corr.).

Weddige[4] had already prepared this quinazoline by fusion of the (*o*)-acet-amino-benzmethyl-amid and by etherification of the

2-methyl-4-oxyquinazoline with alcoholic caustic potash and methyl iodide.

HYDRAZINE ON 6-NITRO-ACETANTHRANIL.

2-Methyl-3-amino-5-nitro-4-ketodihydroquinazoline,

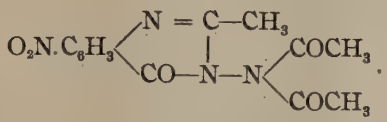


—This is prepared by adding 6-nitro-acetanthranil to the calculated quantity of hydrazine hydrate in 33 per cent. solution. Reaction takes place immediately, as is shown by the heat developed and the change in color from white to yellow. After boiling several minutes to convert any amide to quinazoline, the solution is evaporated almost to dryness and filtered. The crude amino-quinazoline, slightly yellow in color, is then washed with dilute acetic acid to remove any excess of base. The reaction product is then extracted several times with water and finally with a mixture of alcohol and water. This affords a separation of the amino-quinazoline from diquinazolyl which is always formed. On evaporating the combined extracts to small bulk and allowing the solution to stand, beautiful long pink prisms of the amino-quinazoline are obtained. On recrystallization from 50 per cent. alcohol in the presence of bone-black, the amino-quinazoline is obtained in pure condition in long white prisms melting at 152–153° (corr.). The quinazoline is moderately soluble in water, alcohol and acetone, slightly soluble in chloroform and benzene and almost insoluble in ether. Found: C, 48.91, 48.86; H, 3.60, 3.51; N, 25.46, 25.43. Calculated for $C_9H_8O_3N_4$,: C, 49.09; H, 3.63; N, 25.45.

Hydrochloride—Hydrochloric acid is added to a saturated water solution of the quinazoline. Small crystals appear at once and grow to flat glistening plates. If too great an excess of hydrochloric acid is added the crystals are dissolved. The hydrochloride is insoluble in water, but becomes soluble on the addition of a few drops of acid. It is not hydrolyzed by boiling and can be recrystallized without decomposition. It melts at 253–254° (corr.).

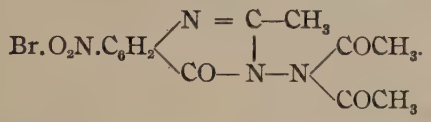
Chlorplatinate.—The amino-quinazoline forms a chlorplatinate when platinic chloride is added to an alcoholic solution acid with hydrochloric acid. Some reduction always takes place and the yellow crystals of the platinum salt are always contaminated with reduced platinum. A pure sample for analysis could not be obtained.

2-Methyl-3-diacetamino-5-nitro-4-ketodihydroquinazoline,



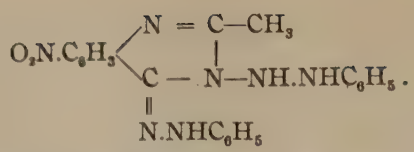
—The amino-quinazoline is dissolved in an excess of acetic anhydride and heated gently. Solution takes place slowly. The excess of anhydride is evaporated and the resulting heavy syrup allowed to crystallize. It is then dissolved in alcohol and allowed to cool slowly. Long, fine white needles of the quinazoline are obtained which melt at 233° (corr.). It is insoluble in water, slightly soluble in hot alcohol and insoluble in the cold. Nitrogen found, 18.74. Calculated for $C_{13}H_{12}O_5N_4$ IV, 18.42.

Brom-2-methyl-3-diacetamino-5-nitro-4-ketodihydroquinazoline,



—On attempting to brominate the amino-quinazoline in water solution, no good product can be obtained. A dark brown, gummy mass is always obtained. Bone-blacking makes no change. The bromdiacetyl derivative is prepared by dissolving the amino-quinazoline in acetic anhydride and adding bromine to the warm solution dissolved in acetic anhydride until, on gentle warming, the solution becomes colorless and the brom derivative precipitates as a white compact powder. The solution is then allowed to cool, the residue filtered off and crystallized from water and alcohol. Small, yellow crystals are obtained which soften at 105° and melt at 170° (corr.). Found: N, 14.93; Br, 20.60. Calculated for $C_{13}H_{11}O_5N_4Br$: N, 14.62; Br, 20.88.

Phenylhydrazone of 2-methyl-3-phenylhydrazino-5-nitro-4-keto-dihydroquinazoline,

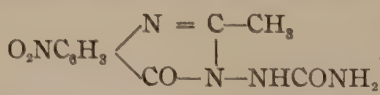


—This derivative can be prepared in two ways: by boiling the amino-quinazoline directly with phenylhydrazine or by dissolving the quinazoline in acetic acid, adding an acetic acid solution of phenylhydrazine and boiling for an hour.

(1) The quinazoline is gently warmed with an excess of phenylhydrazine. When boiling commences, the heat is removed and the reaction progresses of its own accord. Ammonia is split off. It is then boiled for a minute, allowed to cool and acidified with dilute acetic acid. After evaporation to small bulk, alcohol is added and the solution bone-blacked. On standing, large white lustrous plates separate which melt at 124–125° (corr.).

(2) The amino-quinazoline is dissolved in 50 per cent. alcohol and made acid with acetic acid. To this solution excess of phenylhydrazine, dissolved in acetic acid, is added and the mixture boiled for an hour. More alcohol is then added, enough to obtain a clear solution, and the whole allowed to crystallize. The crystals correspond with those obtained by the direct boiling with phenylhydrazine. Nitrogen found, 24.75. Calculated for $C_{21}H_{19}O_2N_7$: N, 24.43.

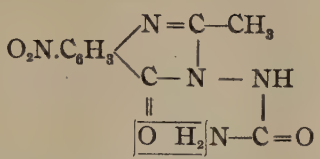
2-Methyl-3-uramino-7-nitro-4-ketodihydroquinazoline,



—This compound could not be obtained by the condensation of the quinazoline with cyanic acid. No reaction took place and the amino-quinazoline was recovered unchanged.

It can be obtained by treating the 4-nitro-acetanthranil with a slight excess of semicarbarized in a saturated water solution. At first no reaction appears to take place but on gentle heating, violent reaction begins and the whole mass turns solid. This is filtered, washed with dilute acetic acid and crystallized from water. Masses of fine silky crystals in clusters result which melt at 266°

(corr.). Nitrogen found, 26 24. Calculated for $C_{10}H_9O_4N_5$: N, 26.61.



By the condensation of the uramino side-chain with the adjacent ketone group by the elimination of water, a new triazine ring would be formed. All attempts to accomplish this result were unsuccessful. The following methods were tried:

(1) Boiling the uramino-quinazoline with phosphorus oxychloride.

(2) Boiling the uramino-quinazoline with phosphorus oxychloride in nitrobenzene solution.

(3) Boiling with a mixture of phosphorus oxychloride and pentachloride.

(4) Boiling with an excess of acetic anhydride.

The first three methods gave no results, charring taking place in each case. With the fourth method, after boiling the uramino-quinazoline in an excess of acetic anhydride for half an hour, solution takes place slowly. When all has gone into solution, it is allowed to cool and the acetic anhydride destroyed by adding water. The acetic acid solution is almost neutralized with caustic alkali and allowed to stand. White crystals of the 2-methyl-3-diaceturamino-7-nitro-4-ketodihydroquinazoline separate and melt at 229–230° (corr.). Nitrogen found, 20.08. Calculated for $C_{14}H_{13}O_6N_5$: N, 20.17.

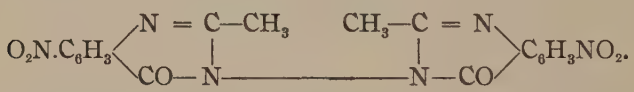
Other reactions of 2-methyl-3-amino-4-ketodihydroquinazoline.— Besides the above, the amino-quinazoline exhibited ther typical aniline reactions. The isonitrile test is given with chloroform and caustic potash. With benzaldehyde, condensation takes place and likely the benzylidene derivatives are formed. The quinazoline is not affected by caustic potash in the cold. On warming, a purple red color develops and the quinazoline goes slowly into solution. No ammonia is given off. On neutralizing this solution with acetic acid, a light yellowish green fluorescent

solution results, from which brownish crystals deposit. These are soluble in water, contain nitrogen and melt at 259–260° (uncorr.) but were not identified.

With nitrous acid the quinazoline forms a diazonium body. In diazotizing, a temperature of 10° was found to be the most satisfactory. The diazo compound couples with dimethylaniline to form a brilliant red derivative, with β-naphthol a brown and with α-naphthol a red. This latter product was isolated. It is obtained by adding a faintly alkaline solution of α-naphthol to the acid diazo solution of the quinazoline, a red body is precipitated at once. This is filtered and crystallized from alcohol. Small brick-red crystals, with a greenish lustre, are obtained. These are insoluble in acids, soluble in alkali to a dark red solution and slightly soluble in alcohol.

On boiling the diazonium compound with water, an oil was obtained which could not be crystallized. When boiled in the presence of hydrochloric acid, fine crystals of metanitraniline were isolated.

2,2′-Dimethyl-5-5-dinitro-4-4′-diketotetrahydrodiquinazolyl,



—In preparing the amino-quinazoline from 6-nitro-acetanthranil and hydrazine the anthranil is added to the hydrazine solution in order to keep the latter in excess and thus obtain a monomolecular reaction (condensation with but one amino group); in preparing the diquinazolyl, on the other hand, the anthranil should always be in excess, thus obtaining a condensation of two molecules of anthranil with one of hydrazine. The hydrazine is added to the finely powdered anthranil with constant stirring and the solution gently heated. The reaction products become yellow in color and changes to a compact mass at the bottom of the beaker. This is filtered and then boiled with water containing alcohol to remove any amino-quinazoline, and finally washed with dilute caustic potash to remove the 6-nitro-acetanthranilic acid formed from the slight excess of anthranil used. The residue consisting of diquinazolyl is crystallized from alcohol

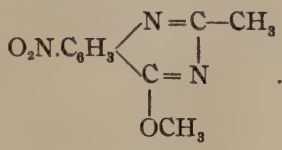
and acetone. It forms small granular crystals which melt at 306° (corr.). It is unaffected by acid or alkali and forms no bromine derivative.

Found: C, 52.32, 52.21; H, 2.89, 2.73; N, 20.35, 20.15. Calculated for $C_{18}H_{12}O_6N_6$: C, 52.74; H, 2.94; N, 20.58.

When the diquinazolyl is dissolved in acetic anhydride and allowed to crystallize, lustrous cubical crystals are deposited which melt at 230°.

OXYGEN ETHERS.

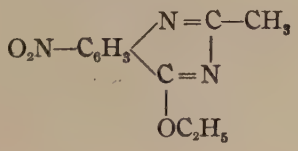
4-Methoxy-2-methyl-5-nitro-quinazoline,



—This is prepared by dissolving 2.5 grams of the 2-methyl-5-nitro-4-quinazolon in 25 cc. methyl alcohol and adding one mole of methyl iodide and one of caustic potash. The mixture is placed in a bomb tube, and heated to 150–160° C. for two to three hours. There is always a high pressure of combustible gas within the tube and the contents of the tube are dark colored from free iodine. A strong odor of ether is always noticeable. The quinazoline is obtained pure by treating the mass, obtained by evaporating the mother-liquor, with sodium bisulphite and extracting the residue with alcohol. On recrystallization and bone-blacking small crystals are obtained melting at 192° (corr.). The corresponding nitrogen isomer melts at 202–203° (corr.). The product melting at 192° is probably not entirely oxygen ether but a mixture of both oxygen and nitrogen ether isomers.

Found: C 54.61, 54.39; H, 4.21, 4.25; N, 19.36, 19.29. Calculated for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.11; N, 19.17.

4-Ethoxy-2-methyl-5-nitro-quinazoline,



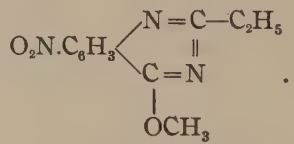
—This was prepared by two methods: First, by dissolving 25 grams of the 2-methyl-5-nitro-4-quinazolon in 25 cc. ethyl alcohol, adding the calculated weight of metallic sodium and then the required amount of ethyl iodide and heating in a bomb to 150–160° as in the methyl derivative. The first four attempts to obtain the ether were unsuccessful, but on the fourth a product melting at 161° (corr.) was obtained.

Second, the ether was also prepared by taking the mixture in (1) and heating it in a small flask under a return condenser. The progress of the reaction was followed by testing its alkalinity with litmus. When the reaction is complete the solution is neutral to litmus. The ether obtained corresponded in it properties with that obtained in first.

Recrystallization from alcohol has no effect on this ether. On treatment with isoamyl iodide, boiling for half an hour, no change was brought about. This was done to see whether the isoamyl iodide added on to the (3) nitrogen and then split off alkyl iodide from the ethoxy group. If this were the case the change from oxygen to nitrogen ethers could readily be explained. The melting-point of the corresponding nitrogen isomer is 208° (corr.) which gives a difference of 47° in melting-points.

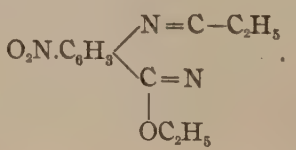
Nitrogen found, 18.24. Calculated for $C_{11}H_{11}N_3O_3$, 18.02.

4-*Methoxy-2-ethyl-5-nitro-quinazoline,*



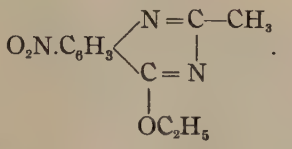
—This derivative could not be obtained by either of the two methods of preparation. In each, the nitrogen isomer was obtained.

4-*Ethoxy-2-ethyl-5-nitro-quinazoline,*



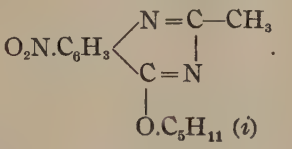
—By the bomb method, a mixture of oxygen and nitrogen ethers was obtained. The crude product in fairly pure condition melted at 167° (uncorr.) but on crystallization from alcohol the melting-point was at once raised to that of the nitrogen isomer. By the second method a product melting 148–149° (uncorr.) was first obtained; on recrystallization, as in the previous case, the melting-point was raised to 180° and the nitrogen isomer obtained. Simple recrystallization from alcohol immediately brought about this change, but the exact cause to which it is due was not ascertained.

4-Ethoxy-2-methyl-7-nitro-quinazoline,



—As in the 5-nitro series this was obtained by method (2). It is unaffected by recrystallization from alcohol and melts at 105–106° (corr.). Nitrogen found, 17.95. Calculated for $C_{11}H_{11}N_2O_3$, 18.02.

4-Isoamyl-oxy-2-methyl-7-nitro-quinazoline,



—This was prepared by both methods, but in neither case was complete reaction obtained. There was always considerable quantities of unchanged methyl hydrogen quinazoline present, which were readily removed by washing with dilute caustic alkali. The residue on crystallization was obtained in large flat plates melting at 104° (corr.). The corresponding nitrogen isomer melts at 117–118°. Nitrogen found, 15.41. Calculated for $C_{14}H_{17}N_3O_3$, 15.27.

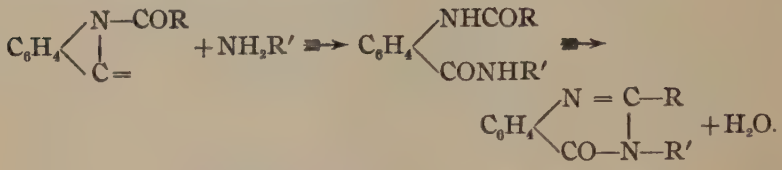
SUMMARY.

(1) Acetanthranils can be obtained directly from the corresponding anthranilic acid by boiling with acetic anhydride.

(2) The ease of formation of acylanthranils decreases with the increase in weight of the entering acyl group.

(3) The nitro-acylanthranils are more reactive than the unnitrated.

(4) Anthranils condense readily with primary amines to form ketodihydroquinazolines. The first product of the reaction is the amide which by loss of water forms the quinazoline. The reaction takes place as follows:



(5) The condensation of hydrazine with the anthranil yields two products,—the amino-quinazolins and the diquinazolyl.

(6) The amino-quinazoline exhibits both the typical quinazoline and the amino reactions.

(7) The ketone group in ketodihydroquinazolines reacts readily with phenylhydrazine.

(8) The 2,3-dialkyl ketodihydroquinazolines readily form salts with the strong acids.

(9) Ketodihydroquinazolines are readily brominated in acetic anhydride solution.

(10) Oxygen ethers are formed by treating the alkaline salt of the 2-alkyl-4-oxyquinazoline with alkyl iodide.

(11) The methyl derivative (10) is abnormal, the nitrogen isomer always resulting.

BIBLIOGRAPHY.

[1] 1878—Griess, Peter: Ber., **11**, 1986. Cyan. quinazolines by action of cyanogen on anthranilic acid.

[2] 1885—Griess, Peter: Ber., **18**, 2417. Reactions of the cyan. quinazoline.

[3] 1885—Weddige, A.: J. pr. (2), **31**, 124. Quinazolines by heating of *o*-acylamino benzamid.

[4] 1887—Weddige, A.: J. pr. (2), **36**, 141. Other methods for obtaining quinazolines from *o*-acylamino-benzamid. Etherification of the alkyl hydrogen quinazoline with alcoholic alkali and alkyl iodide. Proof of structure of the quinazolines obtained.

[5] 1889—Niementowski, S.: J. pr. (2), **40**, 12. Quinazolines by treating homoanthranil amide with acids or acid anhydrides.

[6] —Paal and Busch: Ber., **22**, 2683. Ketoquinazolines by oxidation of the corresponding dihydroquinazolines.

[7] 1890—Dehoff: J. pr. (2), **42**, 346. Nitration and chlorination of the 2-methyl-3-alkyl-4-ketodihydroquinazolines. Also amino derivatives from the chlor-quinazoline.

[8] 1891—Knape, E.: J. pr. (2), **43**, 209. Quinazolines from formyl and oxalyl-(*o*)-amino-benzamid. Methyl iodide addition product. Hydroxy ammonium base.

[9] Zacharias, E.: J. pr. (2), **43**, 432. 8-Nitro-quinazolines from 3-nitro-acetanthranilic acid ethyl ester with primary amines. Reduction to amino.

[10] Thieme, P.: J. pr. (2), **43**, 451. 6-nitro-quinazolines from 5-nitro-acet-anthranilic-acid-ethyl ester with primary amines.

[11] Paal, C., and Krecke, F.: Ber., **24**, 3049. Oxidation of methyl phenyl quinazoline with alkaline potassium permanganate.

[12] 1893—Bischler, A., and Burkart, E.: Ber., **26**, 1349. Quinazolines by heating ammonium salt of acylanthranilic acid.

[13] 1865—Niementowski, S.: J. pr. (2), **51**, 564. Quinazolines by heating anthranilic acid with acid amides.

[14] Bischler, A., and Lang, M.: Ber., **28**, 279. Ketoquinazolines by oxidation of the alkyl quinazoline with chromic acid in acetic acid.

[15] 1897—McCoy, H. N.: Ber., **30**, 1682. Conversion of thio-benzolylene urea to the thio ether and chlor derivative; the latter to the anilino compound.

[16] 1900—Bogert, M. T., and Gotthelf, A. H.: J. A. C. S., **22**, 129. Condensations of anthranilic acid with nitriles to form quinazolines.

[17] 1902—Anschütz Schmidt and Grieffenberg: Ber., **35**, 3480. Acetanthranil and condensations with primary amines to quinazolines.

[18] 1902—Bogert and Hand: J. A. C. S., **24**, 1031. Ketodihydroquinazolines from anthranilic nitrile.

[19] 1903—Pawliewski, B.: Ber., **36**, 2384. Quinazolines by heating anthranilic acid with thio acid amides.

[20] 1904—Thode, C.: J. pr. (2), **69**, 92. Amino-quinazolines by boiling (*o*)-amino-benzhydrazide with acids.

[21] König: J. pr. (2), **69**, 1. Action of nitriles on anthranilic acid.

[22] Gartner, S.: Annalen, **336**, 229. Condensations of benzmetoxazoline with ammonia to form quinazolines. Phenylhydrazine derivatives of the same.

[23] 1905—Bogert, M., and Chambers, V.: J. A. C. S., **27**, 649. Condensations of 6-nitro-acetanthranil with primary amines to form 5-nitro-quinazolines.

[24] Bogert, M., and Steiner, S.: J. A. C. S., **27**, 1327. Synthesis of 7-nitro-quinazolines from 4-nitro-acetanthranil.

[25] 1906—Bogert, M. T., and Hand, W. F.: J. A. C. S., **28**, 94. Preparation of 6-brom-quinazolines from 5-brom-acetanthranil and 5-brom-anthranilic acid.

[26] Bogert, M., and Hoffman, A.: J. A. C. S., **27**, 1293. Quinazolines from homoanthranilic nitrile by warming with alkaline hydrogen dioxide.

[27] Bogert, M., and Chambers, V.: J. A. C. S., **28**, 207. 5-amino-quinazolines by the reduction of the corresponding nitro derivatives.

[28] Gabriel and Colman: Ber., **37**, 3648. Quinazoline, oxidation to pyrimidine-dicarbonic acid.

[29] Heller, G.: Ber., **37**, 3112. Benzoylation of Orexin.

[30] 1901—Bogert and Boroschek: J. A. C. S., **23**, 742. Preparation of 3-nitrophthalic acid.

[31] 1902—Kahn: Ber., **35**, 3866. 6-Nitro-anthranilic acid from 3-nitro-phthalimid.

BIOGRAPHICAL.

Harvey Ambrose Seil entered Columbia University in September, 1899, and graduated in June, 1903, receiving the degree of B.A. In the following year he enrolled as a regular student in the School of Chemistry. During 1904-1906 he did research work in Organic Chemistry and studied for the degree of Ph.D.